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**PATENT**  
**BOX NON-FEE AMENDMENT**

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

In re:	Patent Application of Eva Redei, <i>et al.</i>	: Group Art Unit: Not Yet Assigned : :
Appln. No.:	NOT YET ASSIGNED	: Examiner: Not Yet Assigned : :
Filed:	HEREWITH	: Attorney Docket : No. 048626-5003-01
For:	ANTIDEPRESSANT EFFECTS OF CORTICOTROPIN RELEASE INHIBITING FACTOR	: : (NU99011) :

**PRELIMINARY AMENDMENT**

Preliminary to the examination of the above-captioned application, please amend the application as follows:

**In the Specification:**

On page 1, please amend the CROSS-REFERENCE TO RELATED APPLICATIONS section to recite as follows:

This application is a divisional of U.S. Application No. 09/366,981, filed on August 4, 1999, which claims priority under 35 U.S.C. 119(e) to U.S. Provisional Application No. 60/140,962, filed on June 24, 1999.

Please amend paragraphs 3-6 and 8 on page 3, the paragraph spanning pages 6 and 7, and paragraph 1 on page 8, as indicated on the marked-up copy of the amended specification paragraphs.

Clean copies of the amended paragraphs are attached hereto.

**In the Claims:**

Please cancel claims 1, 2, and 4-16 without prejudice.

Please amend claim 3 to recite as follows. A marked-up copy of claim 3 indicated changes made to the claim is attached hereto.

3. (Amended) A method of treating a depressive disorder in an animal, said method comprising administering to said animal a compound having (Corticotropin Release Inhibiting Factor (CRIF) biological activity, wherein said compound is a peptidomimetic.

Please add claims 17-27 to recite as follows:

17. (New) The method of claim 3, wherein said peptidomimetic comprises at least three amino acids positioned between the fourth and fifth Thyroid Releasing Hormone (TRH) peptide on a pre-pro-TRH molecule.

18. (New) The method of claim 17, wherein said peptidomimetic comprises from three to twenty-two amino acids positioned between the fourth and fifth TRH peptide on a pre-pro-TRH molecule.

19. (New) The method of claim 18, wherein said peptidomimetic comprises the sequence in SEQ ID NO:1.

20. (New) The method of claim 18, wherein said peptidomimetic comprises the sequence in SEQ ID NO:2.

21. (New) The method of claim 18, wherein said peptidomimetic comprises the sequence in SEQ ID NO:3.

22. (New) The method of claim 18, wherein said peptidomimetic comprises the sequence in SEQ ID NO:4.

23. (New) The method of claim 17, wherein said peptidomimetic comprises from three to twenty-six amino acids positioned between the fourth and fifth TRH peptide on a pre-pro-TRH molecule.

24. (New) The method of claim 23, wherein said peptidomimetic comprises the sequence in SEQ ID NO:5.

25. (New) The method of claim 3, wherein said depressive disorder is selected from the group consisting of major depression, minor depression, bipolar disorders, dysthymia, cyclothymia, and premenstrual syndrome.

26. (New) A method of treating a depressive disorder in an animal, said method comprising administering to said animal a compound comprising CRIF or having CRIF-like activity, wherein said compound is delivered to the brain of said animal, and wherein said depressive disorder excludes anxiety, and further wherein said compound is a peptidomimetic.

27. (New) The method of claim 26, wherein said compound is administered to said animal by a route of administration selected from the group consisting of oral, parenteral, intranasal, and central.

### **REMARKS**

Claims 1, 2, and 4-16 have been allowed in U.S. application number 09/366,981, filed August 4, 1999 and are therefore canceled herein. Claims 17-27 have been added herein, and they all depend from amended claim 3. Applicants submit that these claims are supported throughout the as-filed specification, for example, on page 3 and page 7 where specific CRIF fragments are recited and in allowed claims 1, 2, and 4-16. Further, CRIF peptidomimetics and methods of their use are disclosed in the specification at pages 10 and 11.

Specification pages 3, 7, and 8 have also been amended. The pages were amended to include SEQ ID NOs which correspond with the Sequence Listing provided herewith. These amendments do not constitute new matter.

Applicants respectfully and earnestly request timely examination of the above-captioned application.

Respectfully submitted,  
EVA REDEI, *et al.*

December 3, 2001  
(Date)

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Enclosures: Marked-up copy of the Claims as Amended  
Marked-up copy and clean copy of amended paragraphs

1-1517493.1



**Marked up copy of amended specification paragraphs**

Page 1, Cross Reference To Related Applications Section:

This application is a divisional of U.S. Application No. 09/366,981, filed on August 4, 1999, which claims priority under 35 U.S.C. § 119(e) to U.S. Provisional Application No. 60/140,962, filed on June 24, 1999.

Page 3, paragraph 3:

In yet another embodiment, the CRIF peptide comprises the sequence Phe-Ile-Asp-Pro-Glu-Leu-Gln-Arg-Ser-Trp-Glu-Glu-Lys-Glu-Gly-Glu-Gly-Val-Leu-Met-Pro-Glu (SEQ ID NO:1).

Page 3, paragraph 4:

In yet another embodiment, the CRIF peptide comprises the sequence Phe-Ile-Asp-Pro-Glu-Leu-Gln-Arg-Ser-Trp-Glu-Glu-Thr-Glu-Gly-Glu-Glu-Gly-Gly-Leu-Met-Pro-Glu (SEQ ID NO:2).

Page 3, paragraph 5:

In another embodiment, the CRIF peptide comprises the sequence Glu-Gly-Glu-Gly-Val-Leu-Met-Pro-Glu (SEQ ID NO:3).

Page 3, paragraph 6:

In a further embodiment, the CRIF peptide comprises the sequence Leu-Met-Pro-Glu (SEQ ID NO:4).

Page 3, paragraph 8:

In another embodiment, the CRIF peptide comprises the sequence Leu-Ala-Asp-Pro-Lys-Ala-Gln-Arg-Ser-Trp-Glu-Glu-Glu-Glu-Glu-Glu-Glu-Glu-Arg-Glu-Glu-Asp-Leu-Met-Pro-Glu (SEQ ID NO:5).

Pages 6 and 7, spanning paragraph:

The invention should be construed to include any and all CRIF peptides comprising amino acid lengths which range from at least three contiguous amino acids to as much as twenty two amino acids in length, being positioned within the rat prepro-TRH 178-199 molecule. The CRIF peptide of the invention may therefore comprise at least three contiguous amino acids in length, at least four, at least five, at least six, at least seven, at least eight, at least nine, at least ten, at least eleven, at least twelve, at least thirteen, at least fourteen, at least fifteen, at least sixteen, at least seventeen, at least eighteen, at least nineteen, at least twenty, at least twenty one, and up to twenty two contiguous amino acids in length, wherein the peptide is positioned within the rat prepro-TRH 178-199 molecule. Preferably, the CRIF peptide of the invention comprises either four or nine amino acids in length. Preferred rodent CRIF sequence include from three to twenty two contiguous amino acid sequences of the sequence Phe-Ile-Asp-Pro-Glu-Leu-Gln-Arg-Ser-Trp-Glu-Glu-Lys-Glu-Gly-Glu-Gly-Val-Leu-Met-Pro-Glu (full length rat CRIF; SEQ ID NO:1) and the sequence Phe-Ile-Asp-Pro-Glu-Leu-Gln-Arg-Ser-Trp-Glu-Glu-Thr-Glu-Gly-Glu-Glu-Gly-Gly-Leu-Met-Pro-Glu (full length mouse CRIF; SEQ ID NO:2), and also the sequence Glu-Gly-Glu-Gly-Val-Leu-Met-Pro-Glu (a rat CRIF peptide; SEQ ID NO:3), the sequence Leu-Met-Pro-Glu (another rat CRIF peptide; SEQ ID NO:4), and any derivatives and analogs thereof which retain the biological activity of CRIF as defined herein.

Page 8, paragraph 1:

A preferred human CRIF is a peptide having from three to twenty six contiguous amino acids of the sequence Leu-Ala-Asp-Pro-Lys-Ala-Gln-Arg-Ser-Trp-Glu-Glu-Glu-Glu-Glu-Glu-Glu-Glu-Arg-Glu-Glu-Asp-Leu-Met-Pro-Glu (full length human CRIF; SEQ ID NO:5).

**Clean copy of amended specification paragraphs**

Page 1, Cross Reference To Related Applications Section:

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Page 3, paragraph 3:

In yet another embodiment, the CRIF peptide comprises the sequence Phe-Ile-Asp-Pro-Glu-Leu-Gln-Arg-Ser-Trp-Glu-Glu-Lys-Glu-Gly-Glu-Gly-Val-Leu-Met-Pro-Glu (SEQ ID NO:1).

Page 3, paragraph 4:

In yet another embodiment, the CRIF peptide comprises the sequence Phe-Ile-Asp-Pro-Glu-Leu-Gln-Arg-Ser-Trp-Glu-Glu-Thr-Glu-Gly-Glu-Glu-Gly-Gly-Leu-Met-Pro-Glu (SEQ ID NO:2).

Page 3, paragraph 5:

In another embodiment, the CRIF peptide comprises the sequence Glu-Gly-Glu-Gly-Val-Leu-Met-Pro-Glu (SEQ ID NO:3).

Page 3, paragraph 6:

In a further embodiment, the CRIF peptide comprises the sequence Leu-Met-Pro-Glu (SEQ ID NO:4).

Page 3, paragraph 8:

In another embodiment, the CRIF peptide comprises the sequence Leu-Ala-Asp-Pro-Lys-Ala-Gln-Arg-Ser-Trp-Glu-Glu-Glu-Glu-Glu-Glu-Glu-Glu-Arg-Glu-Glu-Asp-Leu-Met-Pro-Glu (SEQ ID NO:5).



Pages 6 and 7, spanning paragraph:

The invention should be construed to include any and all CRIF peptides comprising amino acid lengths which range from at least three contiguous amino acids to as much as twenty two amino acids in length, being positioned within the rat prepro-TRH 178-199 molecule. The CRIF peptide of the invention may therefore comprise at least three contiguous amino acids in length, at least four, at least five, at least six, at least seven, at least eight, at least nine, at least ten, at least eleven, at least twelve, at least thirteen, at least fourteen, at least fifteen, at least sixteen, at least seventeen, at least eighteen, at least nineteen, at least twenty, at least twenty one, and up to twenty two contiguous amino acids in length, wherein the peptide is positioned within the rat prepro-TRH 178-199 molecule. Preferably, the CRIF peptide of the invention comprises either four or nine amino acids in length. Preferred rodent CRIF sequence include from three to twenty two contiguous amino acid sequences of the sequence Phe-Ile-Asp-Pro-Glu-Leu-Gln-Arg-Ser-Trp-Glu-Glu-Lys-Glu-Gly-Glu-Gly-Val-Leu-Met-Pro-Glu (full length rat CRIF; SEQ ID NO:1) and the sequence Phe-Ile-Asp-Pro-Glu-Leu-Gln-Arg-Ser-Trp-Glu-Glu-Thr-Glu-Gly-Glu-Glu-Gly-Gly-Leu-Met-Pro-Glu (full length mouse CRIF; SEQ ID NO:2), and also the sequence Glu-Gly-Glu-Gly-Val-Leu-Met-Pro-Glu (a rat CRIF peptide; SEQ ID NO:3), the sequence Leu-Met-Pro-Glu (another rat CRIF peptide; SEQ ID NO:4), and any derivatives and analogs thereof which retain the biological activity of CRIF as defined herein.

Page 8, paragraph 1:

A preferred human CRIF is a peptide having from three to twenty six contiguous amino acids of the sequence Leu-Ala-Asp-Pro-Lys-Ala-Gln-Arg-Ser-Trp-Glu-Glu-Glu-Glu-Glu-Glu-Glu-Glu-Arg-Glu-Glu-Asp-Leu-Met-Pro-Glu (full length human CRIF; SEQ ID NO:5).